Eur J Vasc Endovasc Surg (2009) **37**, 1–7

Identifying the High-risk Patient with Clinically Relevant Embolisation After Carotid Endarterectomy

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Submitted 7 August 2008; accepted 20 September 2008
Available online 12 November 2008

KEYWORDS
Carotid endarterectomy;
Stroke;
Dextran;
Transcranial Doppler

Abstract *Objectives:* Sustained embolisation after carotid endarterectomy (CEA) predicts an increased risk of stroke due to post-operative carotid thrombosis (POCT). Progression towards stroke can be prevented by transcranial Doppler (TCD) directed intravenous Dextran therapy. However, TCD monitoring is extremely labour intensive. The aim of this study was to see whether a small cohort of high-risk patients could be identified following a 30-min period of monitoring in the Recovery Area of the operating theatre so as to reduce the overall burden of monitoring for the majority of patients.
Methods: Retrospective audit of prospectively acquired data in 821 patients with an accessible temporal window who had undergone 3 h of TCD monitoring after CEA. Patients with >25 emboli in any 10 min period or large emboli distorting the waveform received Dextran.
Results: Group 1: 694 patients (85%) with ≤10 emboli detected within the first 30 min in the Recovery Area of the operating theatre. Recovery: None required Dextran, none suffered a proven ischaemic stroke and none were re-explored. *Group 2*: 127 patients (15%) with 11+ emboli detected. Overall, 26 (20%) required Dextran (54% had the dose increased to control excessive embolisation), none suffered a stroke due to POCT, but 2 suffered embolic strokes despite Dextran. Both, however, had mitigating reasons why optimal Dextran doses could not be administered.
Conclusions: TCD directed Dextran has abolished stroke due to POCT. A high-risk cohort of patients requiring Dextran can be identified by measuring the magnitude of embolisation in the first 30 min in Theatre Recovery. The vast majority of patients (85%) require no further monitoring.

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1078-5884/$34
doi:10.1016/j.ejvs.2008.09.012

Introduction

Despite its proven role in the management of selected patients with symptomatic and asymptomatic disease, carotid endarterectomy (CEA) carries a small but significant risk of peri-operative stroke. Intra-operative stroke (apparent upon recovery from anaesthesia) usually follows inadvertent technical error and is virtually abolished by a targeted strategy of intra-operative monitoring and quality control assessment.[1] By contrast, post-operative stroke is more heterogenous in its aetiology (thromboembolism, hyperperfusion syndrome, intracranial haemorrhage) and more difficult to prevent.

Stroke due to post-operative carotid thrombosis (POCT) is, however, an important cause of post-operative death and persisting neurological disability and was previously considered both unpredictable and unpreventable. However, a number of centres have now demonstrated that stroke due to POCT is preceded by increasing rates of embolisation which can be diagnosed using transcranial Doppler (TCD) ultrasound.[2–9] Evidence suggests that only 3–5% of patients develop clinically relevant post-operative embolisation,[9,10] but about 50% of these 'higher rate embolisers' will suffer a thromboembolic stroke.[4,11]

In Leicester, patients with clinically significant post-operative embolisation (defined as >25 emboli in any 10 min period or 'large' emboli distorting the middle cerebral artery (MCA) waveform) are commenced on intravenous Dextran therapy (20 ml bolus followed by incremental infusion rate starting at 20 ml/h for 12 h).[1] In a series of 500 consecutive patients undergoing CEA, only 4% of patients met these criteria and required Dextran and no-one suffered a stroke due to POCT.[1]

When this protocol was introduced in 1995, 6 h of TCD monitoring was performed.[10] In 1999, this was reduced to 3 h with no associated increase in thrombotic events.[12] Three hours of monitoring is still, however, a considerable burden on resources (especially as >95% of patients will not require Dextran) and it would clearly be preferable to reduce this to the absolute minimum. The impetus for the current study was a growing perception amongst TCD staff that most patients destined to require Dextran did so within their first hour of monitoring, a phenomenon also noted by Abbott *et al*.[9] Accordingly, it was hypothesized that it might be possible to identify a much smaller cohort of higher risk patients within the first 30 min of entering the Recovery Area of the operating theatre. Monitoring could then cease in the remaining 'lower risk' patients.

Methods

A retrospective audit of prospectively acquired data from 1241 consecutive patients undergoing CEA between 1.10.1995 and 31.07.2006 was undertaken. Patients were assessed pre-operatively in a single visit clinic where risk factor management and Duplex assessment was performed. Aspirin (75–150 mg daily) was continued throughout the operative period. Duplex scanning was repeated prior to surgery and all patients had their TCD window checked. The basic technique of CEA (general anaesthesia, systemic heparinisation, loupe magnification and routine shunting, patching and distal intimal tacking) has remained essentially unchanged since 1988.

TCD monitoring was commenced after induction of anaesthesia using a fixed 2 MHz head probe which was protected by a semi-circular headguard. The surgeon and anaesthetist aimed to ensure that mean blood flow velocity in the middle cerebral artery (MCAV) was >15 cm/s at all times. This threshold of 15 cm/s was chosen because Halsey *et al*. has shown this to correlate with loss of cerebral electrical activity.[13] If the MCAV was <15 cm/s following shunt insertion, the shunt was repositioned to exclude abutment against the distal ICA lumen. If the MCAV remained <15 cm/s, blood pressure was therapeutically elevated by the anaesthetist. Immediately prior to patch closure, a 5 mm space was retained adjacent to the orifice of the external carotid artery. The shunt was removed and all vessels back vented and irrigated with heparinised saline. The lumen of the endarterectomy zone was then inspected with a flexible hysteroscope (Olympus 1070-48,). Our policy was to repair all intimal flaps >3 mm and remove any residual thrombi from the lumen.[1]

Following recovery from anaesthesia, the patient was transferred to the Recovery Area of the operating theatre for a 3-h period of TCD monitoring. This was started as soon as possible but there was inevitably a varying time period between awakening the patient in theatre and restarting monitoring in recovery. The Vascular Technologists were experienced in TCD monitoring and used the 1995 Consensus criteria for identifying emboli.[14] Previous work in this department has shown that emboli detected in the post-operative period are exclusively particulate.[15] Dextran 40 (Pharmacia Ltd, Milton Keynes, England) was administered to any patient who had (i) ≥25 emboli in any 10 min period or (ii) emboli which distorted the MCA waveform which suggested that they were large. This threshold of ≥25 emboli per 10-min period was based on work from Gaunt's pilot study.[11] Intravenous Dextran was administered as a 20 ml bolus and then 20 ml/h, increased stepwise every 10 min to a maximum of 50 ml/h if there was no reduction in the rate of embolisation. Once the rate of embolisation stabilised or reduced, Dextran was continued at that dose for a further 12 h.

Definition of post-operative stroke

Any new neurological deficit lasting more than 24 h and which occurred within 30 days of CEA was defined as a post-operative stroke. Where-ever possible, the likeliest cause of the stroke was determined by autopsy and/or CT scanning, Duplex imaging of the extracranial carotid circulation and transcranial Doppler insonation of flow patterns in the circle of Willis. For the purposes of this study, a post-operative stroke was attributed to MCA embolisation from the endarterectomy zone if there was a patent ICA on Duplex imaging, no evidence of a recent myocardial infarction, but a focal area of infarction in the ipsilateral MCA territory irrespective of whether TCD had demonstrated post-operative embolisation. Stroke due to post-operative carotid thrombosis (POCT) was diagnosed where re-exploration and/or Duplex imaging suggested carotid thrombosis. A diagnosis of hyperperfusion syndrome was made in patients who had presented with a new

neurological deficit preceded by either worsening headaches and/or seizures in the absence of embolisation on TCD or haemorrhage on CT scanning. An 'unknown' aetiology was documented in patients who had no evidence of a cardioembolic source and who had also undergone a normal CT scan, extracranial Duplex scan and TCD study.

Results

1241 Patients underwent CEA between 1.10.95 and 31.07.06, of whom 1143 (92%) had an accessible acoustic window to enable TCD monitoring. Although all 1143 patients underwent at least 3 h of post-operative monitoring, only 821 patients (72%) had accurate documentation of the exact amount of embolisation in the first 30 min after monitoring started in the Recovery Area of the operating theatre. Overall, only 26 patients (3.2%) received Dextran according to the protocol. Two other patients received Dextran immediately following restoration of flow (i.e. outwith unit guidelines) at the specific request of the operating surgeon. These two 'off protocol' patients were excluded from analyses.

It was not possible to predict patients destined to require post-operative Dextran based on the magnitude of embolisation detected between the time of final flow restoration and removal of the surgical drapes. Twelve of 26 patients destined to receive Dextran had no emboli detected during this period, 11/26 had 1–10 emboli, while only 3 had >10 emboli detected.

Fig. 1 details the cumulative delay from the patient starting TCD monitoring in the Recovery Area of the operating theatre to starting Dextran therapy (26 patients). Note that 50% of Dextran patients started therapy within 30 min of arriving in recovery. This yield increased to 80% at 60 min and 90% at 90 min. Accordingly, reducing the 'fixed' period of post-operative monitoring to 60 min for all patients would reduce the burden of monitoring (overall) by 2 h, but 20% of patients destined to require Dextran would have been missed. Increasing the period of monitoring to 90 min would identify 90% of patients destined to require Dextran, but would not significantly reduce the overall burden of monitoring. The vast majority of patients would still continue to be monitored for an unnecessarily long time period. Accordingly, this study showed no evidence that simply adopting a shorter fixed time period for everyone (e.g. 30, 60 or 90 min) with no additional discriminating factor (e.g. embolus count) was beneficial to patients.

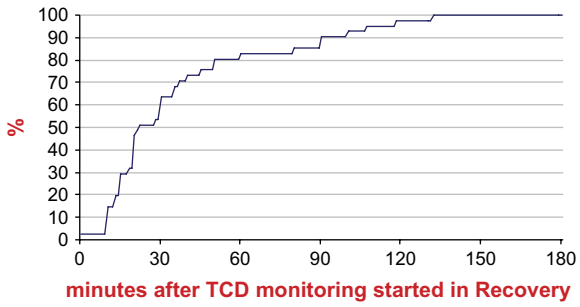

Figure 1 Cumulative time from onset of TCD monitoring in Theatre Recovery to starting Dextran in 26 patients with high rate embolisation.

Table 1 details the number of emboli detected within the first 30 min of monitoring in the Recovery Area of the operating theatre, together with the number of patients who went on to receive Dextran. The majority of patients (424/821 (52%)) had no emboli detected during this 30 min period and none required Dextran. Two hundred and seventy patients (33%) had 1–10 emboli detected and (again) none went on to require Dextran. However, 2/44 patients (4.5%) with 11–20 emboli detected in the first 30 min subsequently developed high grade embolisation and required Dextran. As can be seen (Table 1), an increasing proportion of patients with >20 emboli detected in the first 30 min in Operating Room Recovery went on to receive Dextran.

Table 1 suggests that quantifying the magnitude of embolisation in the first 30 min might identify patients at lowest risk of developing significant post-operative embolisation in whom monitoring could be terminated early. Accordingly, the patient cohort was divided into two subgroups; Group 1 ($n = 694$) included patients who had 0–10 emboli detected in the first 30 min in the Recovery Area of the operating theatre, while Group 2 ($n = 127$) comprised patients with 11+ emboli detected. No patient in Group 1 went on to require Dextran. In Group 2, 26/127 patients (20%) went on to receive Dextran therapy, the dose being increased in 14 (54%) in order to control the rate of embolisation.

Twenty-one patients (2.6%) either died or suffered a stroke within 30 days having made an uneventful recovery from anaesthesia. Table 2 summarises the cause of these events, stratified for the magnitude of embolisation in the first 30 min in the Recovery Area of the operating theatre. Fifteen patients in Group 1 (2.2%) either died or suffered a stroke. Four events were cardiac in origin, six were haemorrhagic, while three followed the hyperperfusion syndrome. Two strokes were classed as being 'unknown' in aetiology. These patients had undergone a normal CT scan, normal TCD study and a normal Duplex scan. While focal

Table 1 Magnitude of embolisation detected in the first 30 min of monitoring in Operating Room Recovery

No of emboli in first 30 min of monitoring in recovery	n = (%)	Number going on to receive Dextran in 3 h
0	424 (52%)	0/424
1–10	270 (33%)	0/270
11–20	44 (5.4%)	2/44
21–30	30 (3.7%)	1/30
31–40	18 (2.2%)	5/18
41–50	9 (1.1%)	1/9
51–60	7 (0.9%)	4/7
61–70	6 (0.7%)	1/6
71–80	3 (0.4%)	2/3
81–90	2 (0.2%)	2/2
91–100	0 (0.0%)	0/0
>100	8 (1.0%)	8/8
	821 (100%)	26/821

Table 2 30-Day death and stroke rate in patients who made a normal recovery from anaesthesia after carotid endarterectomy: stratified for magnitude of embolisation in first 30 min in Operating Room Recovery

Post-operative deaths		Post-operative disabling strokes		Post-operative non-disabling strokes	
Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
<10 Emboli	>10 Emboli	<10 Emboli	>10 Emboli	<10 Emboli	>10 Emboli
15 h Cardiac failure	5d Cardiac arrest	30 h ICH	3 h MCA embolism[a]	18 h Lentiform ICH[e]	3d Hyperperfusion
2d ICH	6d Brainstem stroke[a]	2d Unknown[d]	1 h MCA embolism[a]	24 h Hyperperfusion	
10d Cardiac arrest	9d ICH	3d Cardiac arrest[c]		3d Hyperperfusion	
17d Cardiac failure		3d Bleed into mets[b]		6d Hyperperfusion	
		23d ICH		7d Bleed into infarct	
				14d unknown[d]	
4/694 (0.6%)	3/127 (2.4%)	5/694 (0.7%)	2/127 (1.6%)	6/694 (0.9%)	1/127 (0.8%)

ICH = intracranial haemorrhage.
[a] Patient received Dextran.
[b] MRI scan revealed haemorrhage into diffuse brain metastases (pre-op CT scan reported normal).
[c] Patient suffered a haemodynamic stroke after a cardiac arrest.
[d] CT scan, Duplex and TCD normal: no cause identified.
[e] Bleed into lentiform nucleus after hypertensive crisis.

embolisation cannot be completely excluded, it is important to note that no patient in Group 1 suffered a stroke due to POCT and no one required re-exploration. None of the Group 1 patients received Dextran.

Six patients in Group 2 (4.7%) died or suffered a post-operative stroke. One followed a cardiac event, a second followed brain haemorrhage (no Dextran given), while the third followed the hyperperfusion syndrome. In contrast to Group 1 patients (who suffered no proven ischaemic neurological events), three Group 2 patients (2.4%) suffered ischaemic neurological events, despite receiving Dextran for very high rates of embolisation. None, however, suffered a stroke due to carotid thrombosis (excluded on Duplex assessment) and no Group 2 patient underwent re-exploration. One of the three patients with an ischaemic stroke had high grade MCA embolisation that resolved rapidly with Dextran. However, she was readmitted with an ischaemic brainstem stroke on day 6. It is difficult to see how this could have been prevented. A second patient developed severe, acute heart failure within 1 h of recovery from anaesthesia requiring reintubation and inotropic support. Profuse MCA embolisation was detected, but high dose Dextran could not be administered because of his severe heart failure. In such a situation (where higher dose Dextran is contraindicated), our policy would normally be to consider re-exploration. Unfortunately, this also was contraindicated because of his parlous clinical condition. Uncontrolled high grade embolisation continued and he suffered a disabling stroke 3 h post-operatively. The third patient was extremely agitated following transfer to Theatre Recovery and it proved impossible to apply the TCD probe for 45 min. When monitoring was started, profuse cerebral embolisation was immediately detected. Dextran was started, but within 15 min she suffered a disabling stroke. In hindsight, she had probably sustained considerable earlier embolisation (possibly accounting for her agitation) and the Dextran had little real prospect of exerting any effect in such a short time period.

Finally, seven patients overall (Gp1 = 6, Gp2 = 1) suffered an intracranial haemorrhage ($n = 5$), or a bleed into an existing infarct ($n = 1$) or into cerebral metastases ($n = 1$). None of these patients received Dextran at any time in their care.

Discussion

In a series of themed research projects, this unit has shown that intra-operative stroke tends to follow inadvertent technical error (usually embolism of retained luminal thrombus whose source is bleeding from transected vasa vasorum) which can be virtually abolished by completion quality control assessment.[1] However, stroke due to early post-operative thromboembolism (which traditionally complicates 2–3% of CEAs) appears to be unrelated to technical error.[16] Stroke due to POCT was previously considered to be both unpredictable and unpreventable. However, many centres around the world have now demonstrated that this condition is preceded by increasing rates of embolisation.[2–9] Accordingly, patients at risk of progressing on to stroke due to POCT can be identified using TCD thereby allowing adjuvant pharmacotherapy (e.g. Dextran) to be administered.[1,17]

This study has corroborated earlier findings that a policy of targeted Dextran therapy reduces stroke due to POCT.[1,17] In 821 patients, only three (0.4%) suffered proven ischaemic events following surgery, including the patient with the brainstem event. If the latter is excluded, the incidence of post-operative carotid territory ischaemic stroke falls to 0.24% (a very low risk compared to previous experience). Even if the two 'unknown' aetiology cases are included, the incidence of post-operative ischaemic stroke is still only 0.6%, a value markedly lower than was previously encountered in this unit. It is, however, conceded that two patients did suffer definite ischaemic embolic events despite our TCD/Dextran policy. In both situations, however, there were mitigating circumstances that reduced the potential effectiveness of Dextran. In the first patient, severe acute heart failure prevented the use of a high enough dose of Dextran to control the rate of embolisation. In the second patient, an excessive delay to

starting TCD monitoring in recovery (because of patient restlessness) meant that profuse embolisation went unrecognised. Accordingly, Dextran (when started) had no realistic prospect of preventing the stroke. It is important, however, to emphasise that no patient in this 11-year series has required re-exploration for POCT and Table 2 indicates that where neurological events did occur, they did not follow carotid thrombosis. Prior to 1995, re-exploration for post-operative thrombosis was performed in 2–3% of patients undergoing CEA.[16] These data have to be taken in context with the natural history of patients with high rate embolisation had they not been treated with Dextran. Previous studies suggest that only about 3–5% of patients will develop high rate embolisation after CEA and approximately 50% will go on to suffer a thromboembolic stroke.[4,11] In the current series, 26 patients were found to have high rate embolisation after CEA and received Dextran. Accordingly, thirteen might have been expected to have suffered a thromboembolic stroke, yet only three were observed.

These results therefore suggest that a policy of TCD directed Dextran therapy has reduced the risk of post-operative ischaemic thromboembolic complications and, especially, stroke due to POCT. Interestingly, there is now emerging evidence that a similar strategy may prevent progression on to thromboembolic stroke in patients undergoing carotid angioplasty.[18]

It is accepted, however, that not all centres will be able (or willing) to undertake 3 h of TCD monitoring, especially if it only changes practice in <5% of patients. In 1995, a 6-h period of monitoring was introduced as part of a research project.[10] This was reduced to 3 h in 1999[12] without compromising patient safety. The current study suggests that the optimal monitoring period can be reduced significantly further. Fig. 1 confirms that the majority (80%) of patients destined to require Dextran start their therapy within the first hour of monitoring in Theatre Recovery. Table 1 shows that patients destined to require Dextran can be predicted from the magnitude of embolisation within the first 30 min in Theatre Recovery. In summary, no patient who had fewer than 10 emboli detected in the first 30 min went on to require Dextran, none required re-exploration and none suffered a definite ischaemic neurological event in the post-operative period.

Table 3 shows how a variety of embolus thresholds might influence monitoring practice. If a threshold of >10 emboli in the first 30 min in Theatre Recovery was adopted, monitoring could cease after 30 min in 85% of patients and only 15% would need to be monitored for a longer period of time. Adopting this threshold would mean that no patient destined to require Dextran would have been missed. Conversely, if the threshold for extended monitoring was increased to >20 emboli, only 10% of CEA patients would require extended monitoring, but 8% of patients destined to require Dextran would be missed. If the threshold were increased to >40 emboli, only 4% of patients would undergo extended monitoring, but 35% of patients requiring Dextran would be missed. These data therefore suggest that the optimal policy would be to monitor everyone for 30 min in Theatre Recovery. If the embolus count was ≤10, TCD monitoring could then stop. If the count exceeded 10, then there is a 20% chance that the patient will require Dextran and monitoring should be extended for a further hour. If the threshold for starting Dextran is not met during that time period, monitoring can cease.

Table 3 Yield from varying embolus thresholds for monitoring beyond 30 min in operating room recovery

Number of emboli in first 30 min in recovery	Number monitored	Number of Dextran patients who would have been missed
>10	127/821 (15%)	0/26 (0%)
>20	83/821 (10%)	2/26 (8%)
>30	53/821 (6%)	3/26 (12%)
>40	35/821 (4%)	8/26 (31%)
>50	26/821 (3%)	9/26 (35%)

Unfortunately, the availability of Dextran 40 is now being restricted in several European countries, largely because one of the main suppliers (Baxter Healthcare, Newbury UK) has ceased production. It is, however, still currently manufactured as Rheomacrodex (Meda AS, Allerod, Denmark). Paradoxically, Baxter's decision to withdraw production comes at a time when emerging research suggests that Dextran may be exerting its beneficial effect via an unexpected and quite novel manner. Apart from its well documented antiplatelet and rheological properties, Dextran also appears to cause an increase in plasmin levels due to Dextran blockade of tPA uptake leading to enhanced fibrinolysis, whilst also reducing platelet adhesion to von Willebrand Factor and platelet activation by thrombin.[19] In effect, Dextran may be exerting much of its beneficial effect in the early post-operative period through thrombolysis.

In the event that all sources of Dextran cease, other potential anti-thrombotic agents include S-nitrosoglutathione, (a nitric oxide donor that inhibits platelet adhesion and aggregation)[20] and Tirofiban (intravenous GPIIb/III platelet receptor antagonist).[21] Both have been evaluated in relatively small numbers of CEA patients, but Tirofiban has the advantage of being commercially available (Aggrastat, Merck, Sharpe and Dohme, Hoddeson, UK) and it has also been proposed that it confers benefit in patients 'resistant' to Dextran.[21]

However, an alternative and, perhaps, more relevant strategy is to question why such a small number of patients seem to be prone to developing sustained embolisation following CEA. A number of factors now suggest that it may be the patient who is 'prothrombotic'. First, patients undergoing staged, bilateral CEA have similar rates of embolisation after each procedure (i.e. if you were a higher rate emboliser after the first operation, the same applied after the second and vice versa).[22] Second, in a randomised trial, patch type (prosthetic/vein) had no influence on the incidence of 'high rate' embolisers after CEA.[23] Third, using flow cytometry and platelet aggregation, the platelets of patients who had higher rates of embolisation after CEA were more sensitive to stimulation with ADP.[24] A randomised trial subsequently demonstrated that a single 75 mg dose of Clopidogrel (a potent ADP inhibitor) administered the night before surgery (in addition to normal aspirin therapy) significantly reduced the rate of embolisation after CEA.[25]

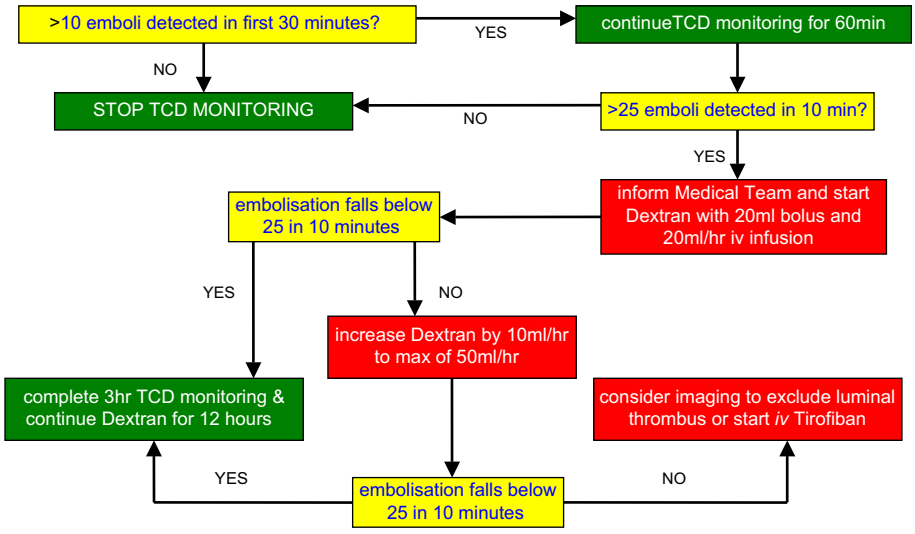

Figure 2 Protocol for post-operative TCD monitoring and administration of Dextran in patients undergoing carotid endarterectomy. The magnitude of embolisation in the first 30 min refers to the number of emboli detected in the first 30 min of monitoring in Theatre Recovery.

Accordingly, since August 2006, it has been the policy of this unit to administer 75 mg Clopidogrel the night before surgery (in addition to routine aspirin). An ongoing audit will subsequently determine whether this will render post-operative TCD monitoring obsolete. Until then, the monitoring protocol currently adopted in the unit is summarised in Fig. 2. All patients currently undergo 30 min of monitoring in the Recovery Area of theatre. If the embolus count is $\leq$10, TCD monitoring ceases. If the number of emboli exceeds 10, TCD monitoring is continued for a further 60 min. If the rate of embolisation does not exceed 25 in any 10-min period during that time, TCD monitoring then ceases. Those few patients meeting the threshold for Dextran therapy are monitored for 3 h. This is because over 50% of patients will require increases in their Dextran dose in order to control the rate of embolisation. Once the magnitude of embolisation has stabilised and is $<$25 in any 10 min period, the Dextran is continued for a further 12 h. Should Dextran fail to control high rates of embolisation, our practice would now be to consider intravenous Tirofiban. To date, however, that has not been necessary.

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